Distinctive clinical features of HPeV-3 infection in 2 neonates with a sepsis-like illness

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We report a human parechovirus-3 (HPeV-3) infection in 2 neonates who had prolonged fever (>5 days) with palmar-plantar erythema. This distinctive rash was observed 4–5 days after fever onset, just before defervescence. Elevated aspartate aminotransferase, lactate dehydrogenase, and ferritin levels were characteristic laboratory findings in the 2 cases, suggesting tissue damage caused by hypercytokinemia. Case 1 was treated with intravenous immunoglobulin, considering the possibility of severe systemic inflammatory responses. The initial ferritin level was 385 ng/mL (range, 0–400 ng/mL); however, the level increased to 2,581 ng/dL on day 5 after fever onset. Case 2 presented with milder clinical symptoms, and the patient recovered spontaneously. HPeV-3 was detected in cerebrospinal fluid and/or blood samples, but no other causative agents were detected. The findings from our cases, in accordance with recent studies, suggest that clinical features such as palmar-plantar erythema and/or hyperferritinemia might be indicators of HPeV-3 infection in neonates with sepsis-like illness. In clinical practice, where virology testing is not easily accessible, clinical features such as palmar-plantar erythema and/or hyperferritinemia might be helpful to diagnose HPeV-3 infection.

Key words: Parechovirus, Newborn, Exanthema, Ferritins

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Introduction

Human parechoviruses (HPeVs) are newly recognized single-stranded RNA viruses that were formerly classified in the Enterovirus genus[1]. Among 16 HPeV serotypes, HPeV-3 infection occurs most frequently among infants below the age of 3 months[2]. Since HPeV-3 was first isolated in Japan in 1999[1], the HPeV serotype has been increasingly identified as an important pathogen of sepsis-like illness and central nervous system infections in neonates and young infants[3]. Life-threatening illnesses such as hemophagocytic lymphohistiocytosis have been reported in neonatal HPeV-3 infection[4]. However, the major clinical features displayed by patients with HPeV-3 infection are also common in those suffering from severe infectious diseases caused by other pathogens[5]. Thus, the diagnosis of HPeV-3 infection is difficult based only on clinical signs.

Recent studies have reported several clinical findings that are characteristic of HPeV-3 infection[4,6-8]. Clinical features such as palmar-plantar erythema and hyperferritinemia might be diagnostic indicators of an HPeV3 infection in febrile neonates and young infants[6,7]. This report describes 2 young infants with an HPeV3 infection who presented

with a prolonged fever, palmar-plantar erythema, and hyper-ferritinemia (>500 ng/mL). These cases may enhance our understanding of the unique features of HPeV-3 infection in young infants.

Case reports

1. Case 1

A 42-day-old male neonate was admitted to Gyeongsang National University of Hospital due to high fever and irritability. He was born at full-term gestational age at a weight of 3,200 g, and he was thriving until this hospital visit. Localized symptoms were not detected, and the results of a physical examination were unremarkable. His healthy older sister was reported to have had a recent febrile respiratory infection. The patient's initial vital signs were as follows: blood pressure 80/50 mmHg, heart rate 168 beats/min, respiratory rate 38 breaths/min, and body temperature 38.8°C. The laboratory findings at admission were as follows: hemoglobin, 9.0 g/dL; white blood cell (WBC) count, 1,990/mm^3; absolute neutrophil count, 670/mm^3; platelet count, 390×10^3/mm^3; aspartate aminotransferase (AST), 42 U/L (range, 22–63 U/L); alanine aminotransferase (ALT), 23 U/L (range, 12–45 U/L); γ-glutamyl transferase (γ-GT), 36 U/L (range, 12–123); creatine kinase (CK), 147 U/L (range, 5–130 U/L); lactate dehydrogenase (LDH), 283 U/L (range, 170–580 U/L); ferritin, 385 ng/mL (range, 0–400 ng/mL); protein, 5.5 g/dL (range, 4.6–7.4 g/dL); albumin, 4.0 g/dL (range, 1.9–5.0 g/dL); and C-reactive protein (CRP), 0.5 mg/L (range, <7.9 mg/L). No cerebrospinal fluid (CSF) pleocytosis or pyuria was observed. Cefotaxime and ampicillin/sulbactam were administered.

No bacteria were found in blood, CSF, or urine samples. HPeV-3 was detected in CSF and serum samples by reverse transcription polymerase chain reaction (PCR) as described in our previous study[9]. CSF PCR tests were negative for herpes, enterovirus, cytomegalovirus, Epstein-Barr virus, and HPeV1. In addition, we found no respiratory viruses such as adenovirus, coronavirus, parainfluenza virus, rhinovirus, respiratory syncytial virus, influenza virus, bocavirus, and metapneumovirus. High fever and irritability persisted. At day 5 of admission, an erythematous rash and swelling were observed on the patient's hands and feet. The laboratory findings were as follows: hemoglobin, 8.7 g/dL; WBC count, 3,930/mm^3; absolute neutrophil count, 260/mm^3; platelet count, 160×10^3/mm^3; protein, 4.4 g/dL; albumin, 2.9 g/dL; AST, 658 U/L; ALT, 162 U/L; γ-GT, 147 U/L; CK, 321 U/L; LDH, 1,324 U/L; ferritin, 2,581 ng/dL; and CRP, 0.3 mg/dL. Intravenous immunoglobulin (IVIG) was administrated because severe systemic inflammatory responses were considered in the patient. After IVIG treatment, the patient's fever subsided gradually and the erythematous rash disappeared. The patient was discharged on day 8 of admission.

2. Case 2

A 25-day-old female neonate was admitted to Gyeongsang National University Hospital due to high fever and poor feeding. She was born without incident at full-term gestational age, and her birth weight was 2,900 g. She had no known sick contacts. The patient displayed abdominal distension and loose stool, but no localized signs and symptoms were noted. The patient's vital signs were as follows: heart rate, 158 beats/min; respiratory rate, 48 breaths/min; and body temperature, 38.4°C. All laboratory findings at the time of admission were within the normal range. No CSF pleocytosis or pyuria was observed. Conservative antibiotics (ampicillin/sulbactam and gentamycin) were administered because the patient appeared ill.

We detected no viruses causing gastroenteritis, including rotavirus, norovirus, astrovirus, and enterovirus, and serologic studies for cytomegalovirus, rubella virus, Toxoplasma, and herpes simplex virus were negative. HPeV-3 was detected in the patient's CSF by PCR, but no other viruses were detected in respiratory or CSF specimens. An erythematous rash and edema were observed on the patient's hands and feet at day 4 of admission (Fig. 1), with

Fig. 1. Images of the erythematous and edematous rash on the hands and feet of case 2.

the rash being more obvious on her feet. Fever persisted for 5 days of admission. The laboratory findings on day 5 of admission were as follows: hemoglobin, 13.9 g/dL; WBC count, 12,810/mm^3; absolute neutrophil count, 1,690/mm^3; platelet count, 161×10^3/mm^3; AST, 317 U/L; ALT, 75 U/L; γ-GT, 238 U/L; LDH, 946 U/L; ferritin, 630 ng/mL; and CRP, 0.6 mg/dL. The patient's fever gradually subsided at day 6 of admission without IVIG administration. The patient was discharged on day 7 of admission.

Discussion

Here, we report HPeV-3 infection in 2 neonates who had prolonged fever with palmar-plantar erythema. Elevated AST, LDH, and ferritin levels were characteristic laboratory findings in both cases, suggesting tissue damage caused by hypercytokinemia. IVIG was administered in case 1 because severe systemic inflammatory responses were considered in the patient. Case 2 displayed a milder clinical presentation, and the patient recovered spontaneously.

Although HPeV-3 has been known for only a decade, this virus has attracted the concern and attention of pediatricians. Associations between this virus and severe diseases such as sepsis-like illness and meningoencephalitis in neonates and young infants have been widely described[3]. However, the principle features of sepsis-like conditions are also common in severe infectious diseases caused by other pathogens, particularly enteroviruses. A prospective study showed that it was not possible to distinguish neonatal HPeV infection (most are HPeV-3) from enterovirus infection on the basis of clinical signs[5]. Although an association between a distinctive pattern of white matter injury and HPeV-3 encephalitis has been suggested[10], this pattern is also seen in enterovirus meningoencephalitis[11]. PCR is commonly used to diagnose viral infections; however, PCR for HPeV-3 is not commercially available[6]. Thus, the diagnosis of HPeV-3 infection is difficult in current clinical practice. In Korea, only a few studies have been conducted on clinical features of HPeV-3 infection[9].

Recently, distinctive clinical features, including palmar-plantar erythema and hyperferritinemia, have been suggested as diagnostic indicators of an HPeV-3 infection[4,6-8]. Although a rash was known to frequently accompany HPeV-3 infection[2], the characteristics of the rash attracted little attention as a diagnostic clue. Recent studies have described distinctive palmar-plantar erythema or reddening of skin rashes in neonates and infants with an HPeV-3 infection[4,7]. As observed in our study, the characteristic rash is erythematous and limited to the palms and soles[4,7]. Yuzurihara et al.[4] reported nine neonates and infants with HPeV-3 infection. The median age of onset in the patients was 31 days[4]. In 5 of 9 patients (55%), palmar-plantar reddening appeared on day 3 after fever onset, on average, and fever persisted for 3-5 days (median, 4 days)[4]. Shoji et al.[7] also reported palmar-plantar erythema in 12 of 15 neonates (80%) and young infants with an HPeV-3 infection. The median age of onset was 33 days (range, 10-81 days)[7]. Fever persisted for a median of 3 days (range, 1-4 days), and the distinctive skin rash developed at a mean of 3 days (range, 1-5 days) after fever onset[7]. In our cases, the rash developed at 4-5 days after fever onset. Thus, palmar-plantar erythema or reddening seemed to develop just before defervescence, approximately 3-5 days after fever onset. This pattern of fever and rash is also seen in exanthema subitum caused by human herpes virus (HHV)-6[12]. HHV-6 viremia can be detected during the febrile period (after 2 days of illness, before the onset of the rash), and anti-HHV-6 antibodies are first detected around the time of the rash onset (3 days of illness)[12]. The rash in exanthema subitum is thought to result from antigen-antibody complexes[12]. A similar pathogenic mechanism of exanthem subitum might function in the rash observed with HPeV-3 infection. If so, palmar-plantar erythema might be a sign of clinical improvement in patients with an HPeV-3 infection. Or, microvascular endothelial cells of the palms and soles might be susceptible to this virus. Compared with other HPeVs, HPeV-3 is known to use a different receptor to enter cells[2]. However, there are no studies about immediate antibody responses after HPeV-3 infection as well as susceptibility of this virus to microvascular endothelial cells of the palm and soles. The pathogenesis of the distinctive rash in HPeV-3 infection is still unknown.

Hyperferritinemia seems to be another diagnostic clue for HPeV-3 infection. A recent study showed that the ferritin level was significantly higher in patients with HPeV-3 infection (mean, 2,437 ng/mL) than in those infected with other pathogens, including enterovirus (mean, 552 ng/mL) and respiratory syncytial virus (mean, 237 ng/mL)[6]. They suggested that ferritin level over than 1,000 ng/mL might be significant findings of HPeV-3 infection[6]. Ferritin levels were high on days 4-5 after fever onset[6], consistent with the time of defervescence. That study also found that the WBC and platelet counts were significantly lower in HPeV-3 infection than in other infections[6]. Yuzurihara et al.[4] also showed high level of ferritin (median, 2,307 ng/mL) and LDH (median, 643 U/L) in neonates with HPeV-3 infection. Hyperferritinemia, cytopenia, and/or high LDH are assumed to reflect hypercytokinemia[6]. Based on these findings, they suggested HPeV-3 infection should be considered possible causes of hypercytokinemia[4,6]. The laboratory findings in our 2 cases were similar to the previous studies[4,6] and characterized by elevated markers of tissue injury, including AST, LDH, and ferritin. Prolonged fever over than 5 days was observed in both 2 cases. Thus, as suggestion of the previous studies[4,6], hypercytokinemia might contribute to clinical and laboratory features of our cases, which can be interpreted with severe systemic inflammatory response to HPeV-3 infection.

Management of HPeV-3 infection is limited to supportive care. There are no effective antiviral drugs against HPeV[13]. IVIG have been used as supportive therapy in the severe cases of HPeV infection based on potential benefit in early IVIG treatment of severe enterovirus infection[13]. An anecdotal report showed successful IVIG treatment of HPeV-1 infection in myocarditis in a young infant[13]. Some researchers suggested that IVIG might be an option for preventing or treating severe HPeV-3 infection based on lower titers of neutralizing antibody in young infants with severe disease related to this virus[14]. Commercially available IVIG seems to contain high titers of neutralizing antibody against HPeV-3[14]. However, a recent study showed most HPeV-3 strains might be difficult to neutralize *in vivo* by IVIG[15]. Thus, it is unclear whether IVIG is a useful treatment for HPeV-3 infection. In our case, IVIG was administrated at 5th days of fever, which was coincides with the timing of the end of fever in patients with HPeV-3 infection of other studies (fever duration, 3–5 days). Thus, we do not conclude whether IVIG is responsible in symptoms improvement in our case 1 or not. Considering disease severity in neonatal HPeV infection, development of antiviral agent and randomized studies to prove the efficacy of IVIG treatment in HPeV-3 infection will be necessary.

In clinical practice where virology testing is not easily accessible, clinical features like palmar-plantar erythema and/or hyperferritinemia might be helpful to diagnose HPeV-3 infection. We recommend testing for ferritin in febrile neonatal patients with palmar-plantar erythema. However, additional studies will be necessary to demonstrate the diagnostic value of these features in HPeV-3 infection. If these findings are unique to HPeV-3 infection, pathogenic mechanisms should be studied.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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